Children in Research

Goal: To develop an analysis of the ethics of research with children, and assess specific ethical issues that arise in the conduct of research with children using empirical methods.

Section: Human Subjects Research- Unit on Vulnerable Populations

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Background: Recent findings that the majority of medications have not been approved for use in children have reinforced the importance of conducting pediatric research. In addition, several Federal initiatives encourage pediatric research. First, the NIH has issued a policy that requires the inclusion of children in a broad range of research (NIH 1998). In addition, the FDA offers 6 months additional marketing exclusivity to firms that submit data pertaining to the use of tested agents in pediatric populations.

At the same time, the debate over whether and when it is ethical to enroll children in research is at least 30 years old, and remains unsettled. Some commentators argue that pediatric research necessarily exploits children. Others defend pediatric research on the grounds that children would consent to it if they could, and participation may help children medically, or teach them the importance of altruism.

In contrast to the widespread debate over the ethical appropriateness of pediatric research in general, there has been little discussion concerning precisely what safeguards should be in place for pediatric research. Most of the existing literature focuses on the existing Federal regulations governing pediatric research. The Federal regulations apply additional safeguards to pediatric research as the risk/benefit ratio becomes less favorable to subjects. In particular, the Federal regulation describe 3 risk/benefit categories: 1) minimal risk research; 2) research that poses greater than minimal risk, but offers a prospect of direct benefit; and 3) research that poses greater than minimal risk and does not offer a prospect of direct benefit.

The Federal regulations define minimal risk as the risks of everyday life. A number of writers have argued that this definition is unclear, and difficult to implement. Largely absent from the literature is any discussion of which potential benefits can justify the risks of research. That is, which potential benefits count as "direct" benefits. This question has taken on increased importance following an OHRP ruling that the psychological or altruistic benefit that a child receives from donating bone marrow to a sick sibling constitutes a direct benefit. Finally, there is no data on how IRBs interpret the Federal regulations, nor on how children understand research.

Objectives:

1) To assess the ethical acceptability of pediatric research, and develop an ethical framework for non-beneficial research in children.

2) To assess the extent to which the existing Federal regulations for pediatric research provide appropriate protections, and whether they allow placebo controlled trials.

3) To assess empirically how IRBs interpret and implement the Federal regulations governing research with children.

4) To assess empirically the extent to which children want to be involved in the research decision making process, and how they understand research.

5) To evaluate existing accounts of risks standards for non-beneficial research with children, and develop an account of an appropriate standard.

6) To develop an analysis of 'direct' benefits within the context of pediatric research

Methodology: We began by gathering and analyzing the existing literature on the ethics of pediatric research. Based on this literature, we developed a conceptual typography of the salient ethical issues, and determined what methods were needed to address them. Our analysis distinguishes the general question of whether it is acceptable to expose children to research risks for the benefit of others, from specific questions about which safeguards should apply to pediatric research.

Most commentators agree that pediatric research is acceptable when the direct benefits to subjects justify the risks. This consensus has focused debate on 'non-beneficial' pediatric research, that is, research for which the direct benefits to subjects do not justify or 'outweigh' the risks.

The Federal regulations allow non-beneficial pediatric research under certain conditions, and non-beneficial pediatric research is widely practiced. However, no one has yet developed a sufficient ethical justification for it. The importance of developing such a framework has been underscored by the Maryland Court of Appeals' recent ruling in *Grimes v. Kennedy Krieger Institute* that all non-beneficial pediatric research in the state of Maryland is illegal.

Most assessments assume, sometimes implicitly, that non-beneficial pediatric research is *sui generis*, and requires its own, independent ethical justification. Since this approach has yielded few results, our approach is to compare pediatric research to the treatment of children in ordinary life. Unlike the research setting, exposing children to some risks for the benefit of others is widely accepted in daily life. Commonplace examples include parents directing their children to shovel the walk of an infirm neighbor or help a young child cross the street. More dramatic examples include children being instructed to rescue drowning infants. Assessment of this aspect of ordinary life may determine whether, and under what conditions, including what levels of risk, non-beneficial pediatric research is ethically acceptable.

The actual conduct of most pediatric research is governed by the Federal regulations, which include specific requirements for research with children. The protections included in the Federal regulations are based on the risk/benefit profile of specific studies. Under the regulations, children may be enrolled in research as long as the risks are no more than a minor increase over 'minimal,' or the potential 'direct' benefits justify the risks. The Federal regulations define 'minimal' risks as the risks "ordinarily encountered in daily life." This standard is justified on the grounds that as long as the risks are no greater than those present in daily life, enrolling children in research will not increase the risks to which they are exposed. Hence, minimal risk research is *prima facie* ethically acceptable. There has been much debate over whether this definition is sufficiently clear. However, there are no data on how IRBs actually interpret and implement it.

The Federal regulations allow children to be enrolled in non-beneficial research only when the children provide their 'assent", defined as a positive agreement. However, the pediatric regulations, unlike the regulations governing research with adults, leave the content of the assent process—what children should be told, how their assent should be obtained—up to the discretion of the reviewing IRB. In general, then, the extent to which the Federal regulations provide appropriate protection for children

depends a great deal on how they are interpreted and implemented by IRBs. Unfortunately, we have no data on how IRBs understand the pediatric regulations.

To develop data in this regard, we conducted a telephone survey of 188 IRB chairpersons around the country. This survey was designed to assess: 1) how IRBs interpret the minimal risk standard; 2) how they implement the assent requirement; and 3) how they understand 'direct' benefits. We targeted three groups of IRBs: 1) IRBs that primarily review pediatric research, identified through the Association of Medical School Pediatric Department Chairs (AMSPDC) and National Association of Children's Hospitals and Related Institutions (NACHRI) membership lists; 2) Independent IRBs identified through the Health Industry Manufacturers Association (now called AdvaMed) list, and; 3) Randomly selected IRBs identified from an Office for Human Research Protections list of all IRBs that have a multiple project assurance.

Next, the Federal regulations require the permission of the child's parents and, in most cases, the assent of children who are capable of providing it. In the absence of explicit guidance from the Federal regulations, it is generally assumed that children become capable of providing assent at the age of 7. This assumption traces largely to the decades old "rule of 7s" which stipulates that children under 7 cannot make their own decisions, children 7-14 years of age can make relatively minor decisions, and children over age 14 have decisionmaking capacity essentially equivalent to adults. There has been no recent analysis to assess the appropriateness of this guideline. We undertook an analysis of the justification for requiring children's assent.

The Federal regulations allow children to be enrolled in non-beneficial research that poses more than minimal risk only when it is likely to yield generalizable knowledge about the subject's disorder or condition. This 'subject's condition' requirement was first endorsed by Hans Jonas, in one of the classic papers on research ethics (Philosophical Reflections on Experimenting with Human Subjects, 1969). Jonas argued that this requirement increases the chances that individuals are enrolled in research only when their participation is necessary, and they are likely to identify with the goals of the research. We developed a conceptual analysis to assess whether the subject's condition requirement effectively realizes these important protections.

Finally, there is very little information concerning children's understanding of research, the extent to which they want to participate in the research decision making process, and the extent to which they actually participate in this process and agree with the decisions that their parents make. These questions suggest the need for an in-depth survey of children who are actually participating in research.

Results: The analogy to exposing children to risks for the benefit of others in everyday life suggests that non-beneficial research may be ethically acceptable. However, this analogy suggests that the Federal regulations definition of minimal risk is not simply unclear, but mistaken. Many of the risks to which children are exposed in daily life are justified by the potential for direct benefit. Thus, this level of risk does not justify exposing children to the same level of risk in non-beneficial research. Instead, the proper standard for non-beneficial research should be the risks to which children may be exposed in daily life to help others.

Our survey of IRB chairpersons suggests that the minimal risk standard is conservative. In particular, when given a list of research procedures, only a single blood draw was deemed minimal risk by a majority of IRB chairpersons. Other procedures, including MRI, a survey of sexual behavior, and LP, were deemed more than minimal risk by many chairpersons. These results raise questions about the extent to which IRBs are stopping non-beneficial pediatric research as too risky, or regarding it has having sufficient potential benefit to justify the risks. In addition, IRBs have very different views of the ethics of payment for pediatric research, and many IRBs are willing to enroll infants even when the research could be conducted with older children. To provide IRBs with guidance on payment, we have developed a framework for pediatric payment (described in the payment summary).

Our survey also reveals that, in the absence of explicit guidance on the assent process for children, IRBs provide children with the same information that must be provided to adults. The primary exception is that many IRBs do not inform children of the rare, serious risks of research participation. These results raise questions about the extent to which the regulations for adults are appropriate for children. To take one example, Schwartz found that children who are informed they are participating in research are more anxious. If correct, these results would raise questions about the extent to which children should be informed of this information.

Recent data suggest that children do not understand the concept of altruism until 12-14 years of age. This is important because the primary purpose of research is to develop knowledge to help others. This suggests that children under 12 years of age cannot appreciate the purpose of research, hence, are not capable of providing assent. Based on such data, we recommend that the standard for assent should be raised to age 12-14. However, making this change alone would result in many children having no say in whether they participate in research, including non-beneficial research. To remedy this concern, we recommend that the regulations adopt an independent ‘dissent’ requirement for pediatric research.

Our survey of IRB chairpersons suggests that the subject's condition requirement is confusing. In particular, there is widespread disagreement over what constitutes a condition under the requirement. In addition, analysis suggests that the requirement does not ensure children are enrolled in research only when their participation is necessary. For instance, this requirement allows children with asthma to be enrolled in early phase toxicity testing of a new asthma drug, even when the research could be conducted by enrolling only adults. To address this gap, we recommend that the regulations adopt an explicit 'necessity' requirement: children should not be enrolled in research unless the research cannot be conducted with adults who are able to consent.

Analysis of the Grimes ruling highlights a major gap in human subjects protections. It has been widely assumed that the Federal regulations establish when it is lawful to conduct human subjects research, including pediatric research. In fact, the Federal regulations establish only how research must be conducted to receive Federal funding or approval. Courts are under no obligation to find that research meeting the Federal regulations is lawful. To address the possibility that other courts or state legislatures may follow the precedents set in Maryland, and develop their own rules for when it is lawful to conduct pediatric research, we recommend development of laws governing pediatric research by legislation, or model statute.

Future Directions: Most of the literature on the ethics of pediatric research focuses on non-beneficial pediatric research. The assumption has been that research is *prima facie* acceptable as long as the 'direct' benefits justify the risks. Despite this consensus, there has been no analysis of what constitutes a direct benefit. For instance, OHRP has found that the possibility of helping a sibling can justify the risks of enrollment in a bone marrow donor protocol. This ruling raises difficult questions. What about the possibility of helping individuals who are not 1st degree family members, such as cousins or close friends? What about clinically indicated counseling, or the chance that a research scan might reveal a treatable tumor? To answer these questions, we plan to develop a systematic assessment of which benefits can justify the risks of pediatric research.

The ethical debate over *non*-beneficial research has been going on for over 30 years, and remains unsettled. We plan to develop an ethical framework to justify non-beneficial pediatric research on the basis of the treatment of children in everyday life. In particular: what risks may children be exposed to in daily life to help others? To assess children's actual and preferred role in the research decisionmaking process, we are planning an in-depth survey of children and one of their parents in order to evaluate empirically children's understanding and role in making decisions concerning their participation in clinical research. For this study, we will conceptualize children's involvement in the decision-making process in terms of 5 elements: 1) receipt of information concerning the available options ; 2) understanding of this information; 3) assessment of the available options; 4) expression of a preferred option; and 5) coordination with parental decision-making. Finally, as part of this study, we will also assess why parents enroll their children in research, and which parents do this.